

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
3 April 2003 (03.04.2003)

PCT

(10) International Publication Number  
**WO 03/027275 A1**

(51) International Patent Classification<sup>7</sup>: C12N 9/99

(21) International Application Number: PCT/US02/30059

(22) International Filing Date:  
23 September 2002 (23.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/325,390 27 September 2001 (27.09.2001) US

(71) Applicant (for all designated States except US): **ALCON, INC.** [CH/CH]; P. O. Box 162, Bösch 69, CH-6331 Hünenberg (CH).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HELLBERG, Mark, R.** [US/US]; 2545 Glen Ridge Drive, Highland Village, TX 75077 (US). **CLARK, Abbot, F.** [US/US]; 5603 Rachel Court, Arlington, TX 76017 (US). **PANG, Iok-Hou** [US/US]; 125 Starbridge Lane, Grand Prairie, TX 75052 (US). **HELLBERG, Peggy, Elizabeth** [US/US]; 2545 Glen Ridge, Highland Village, TX 75077 (US). **MCNATT, Loretta, Graves** [US/US]; 224 Baker Drive, Hurst, TX 76054 (US). **WANG, Wan-Heng** [CN/US]; 2805 Woodland Hills Drive, Grapevine, TX 76051 (US).

(74) Agents: **SCHULTZ, Teresa, J.** et al.; Alcon Research, Ltd., R & D Counsel, Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).

**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR)
- of inventorship (Rule 4.17(iv)) for US only

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/027275 A1

(54) Title: INHIBITORS OF GLYCOGEN SYNTHASE KINASE-3 (GSK-3) FOR TREATING GLAUCOMA

(57) Abstract: The use of inhibitors of GSK-3 useful for treating glaucoma is disclosed.

**IN THE UNITED STATES PATENT  
AND TRADEMARK OFFICE**

**INHIBITORS OF GLYCOGEN SYNTHASE KINASE-3 (GSK-3)  
FOR TREATING GLAUCOMA**

5                   The present invention is directed to inhibitors of glycogen synthase kinase-3 for  
10       lowering and controlling normal or elevated intraocular pressure (IOP) and treating  
      glaucoma.

**Background of the Invention**

15           The disease state referred to as glaucoma is characterized by a permanent loss of  
      visual function due to irreversible damage to the optic nerve. The several morphologically  
      or functionally distinct types of glaucoma are typically characterized by elevated IOP,  
      which is considered to be causally related to the pathological course of the disease. Ocular  
      hypertension is a condition wherein intraocular pressure is elevated, but no apparent loss  
20       of visual function has occurred; such patients are considered to be a high risk for the  
      eventual development of the visual loss associated with glaucoma. Some patients with  
      glaucomatous field loss have relatively low intraocular pressure. These so called  
      normotension or low tension glaucoma patients can also benefit from agents that lower and  
      control IOP. If glaucoma or ocular hypertension is detected early and treated promptly  
25       with medications that effectively reduce elevated intraocular pressure, loss of visual  
      function or its progressive deterioration can generally be ameliorated. Drug therapies that  
      have proven to be effective for the reduction of intraocular pressure include both agents  
      that decrease aqueous humor production and agents that increase the outflow facility.  
      Such therapies are in general administered by one of two possible routes, topically (direct  
30       application to the eye) or orally.

There are some individuals who do not respond well when treated with certain existing glaucoma therapies. There is, therefore, a need for other topical therapeutic agents that control IOP.

5     **Summary of the Invention**

The present invention is directed to inhibitors of GSK-3 which can be used to treat glaucomatous optic neuropathy and/or lower and control IOP associated with normal-tension glaucoma, ocular hypertension, and/or glaucoma in warm blooded animals,  
10     including man. The compounds are formulated in pharmaceutical compositions suitable for topical delivery to the eye.

**Description of the Preferred Embodiments**

15     Elevated intraocular pressure (IOP) is often an indicator of glaucoma. Left unchecked, continual and long term elevated IOP can contribute to the progressive deterioration of the retina and the loss of visual function. Therefore, lowering IOP is often an objective in the treatment of glaucoma patients in order to decrease the potential for or severity of glaucomatous retinopathy. It has been shown that even those glaucoma  
20     patients who do not exhibit elevated levels of IOP benefit from agents that lower and control IOP. Unfortunately, some individuals do not respond well when treated with certain existing glaucoma therapies.

Wnt proteins comprise a large family of structurally related ligands that activate  
25     the Wnt signaling pathway. The frizzle family of proteins are key components in this pathway serving as membrane bound receptors for Wnt. The frizzle proteins are a family of seven transmembrane proteins that have an N-terminal extracellular cysteine rich domain and a cytoplasmic carboxylate tail. Binding of Wnt to frizzle initiates a cascade of events one of which results in the inhibition of (GSK-3) preventing the phosphorylation of  
30      $\beta$ -catenin. Phosphorylation of  $\beta$ -catenin leads to its degradation. Activation of the Wnt pathway increases the intracellular concentration of uncomplexed  $\beta$ -catenin which can

activate  $\beta$ -catenin- T cell factor/Lymphoid enhancer factor (TCF/Lef) dependent gene transcription.

Frizzled Related Proteins (FRP) are a family of secreted proteins with cysteine rich regions that are homologous to those of the frizzle family of proteins but lack the membrane-spanning segments of the frizzle proteins. The secreted FRP acts to antagonize the Wnt signaling pathway by binding extracellular Wnt and preventing it from interacting with frizzle proteins or by forming a nonfunctional complexes with the frizzled receptor. Bafico *et al.* (1999).

Recently it has been discovered that frizzled related protein (FRP) is differentially expressed in a number of glaucomatous trabecular meshwork cell lines. Perfusion of FRP-1 through perfused human ocular anterior segments maintained in culture resulted in a decrease in flowrate and a corresponding decrease in  $\beta$ -catenin protein levels in the ciliary body and the trabecular meshwork (TM). The decreased flow rate in the cultured anterior segments models an increase in resistance to outflow (increase in intraocular pressure) in intact eye. These results show that there is an active Wnt signaling pathway in the TM and ciliary body and suggest that this pathway is responsible at least in part for maintaining outflow through the TM and thereby controlling IOP.

Since the intracellular level of  $\beta$ -catenin is at least partially regulated by its phosphorylation by GSK-3, inhibition of GSK-3 results in the increase in uncomplexed soluble  $\beta$ -catenin irrespective of the levels of FRP. GSK-3 inhibitors circumvent the FRP mediated antagonism of the Wnt signaling pathway caused by the elevated levels of FRP and counteract the increase in outflow resistance that results from the increase in production of FRP in individuals with glaucoma.

Increased expression of FRP was also detected in the retinas from human donors having retinitis pigmentosa (RP). RP is a family of degenerative diseases that effect the photoreceptors and causes blindness. Since FRP stimulates apoptosis in neurons *in vitro* the presence of elevated FRP suggests that FRP mediated disruption of Wnt signaling may

be involved in retinal degeneration. Although glaucoma is the selective loss of retinal ganglion cells and not photoreceptor cells toxicity mediated by increased expression of FRP or by other mechanism governed by a GSK-3 mediated pathway may contribute to the loss of retinal ganglion cells in glaucoma. Therefore GSK-3 inhibitors would treat the  
5      loss of retinal ganglion and also reduce intraocular pressure by increasing aqueous humor outflow.

While not being bound by theory the inventors believe that inhibition of GSK-3 will lower and control normal or elevated intraocular pressure (IOP) and treat  
10      glaucomatous optic neuropathy. Compounds that act as GSK-3 inhibitors are well known and have shown a variety of utilities, primarily for disorders or conditions associated with diabetes, dementias such as Alzheimer's disease and manic depression. U.S. Patent No. 6,057,117 discloses the use of selective inhibitors of GSK-3 for the treatment of diseases that are mediated by GSK-3 activity including diabetes mellitus. WO 00/38675 discloses a  
15      method of treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, manic depression, mood disorders such as schizophrenia, neurotraumatic disorders such as acute stroke, hair loss and cancer. WO 00/21927 discloses certain pyrrole-2,5-dione derivatives that are GSK-3 inhibitors for the  
20      treatment of diabetes, dementias such as Alzheimer's disease and manic depression. WO 01/56567 describes 2,4-dimainothiazole derivatives and their use as GSK-3 inhibitors, WO 01/49709 describes peptide inhibitors of GSK-3, WO 01/47533 discloses the development of modulatory strategies for the treatment of various diseases. WO 01/41768 discloses the use of hymenialdisine or derivatives for inhibiting cyclin dependent kinases, GSK-3 beta  
25      and casein kinase 1 for treating neurodegenerative disorders such as Alzheimer's disease, diabetes, inflammatory pathologies and cancers. WO 01/37819 discloses the use of indirubine derivatives for making medicines inhibiting GSK-3 beta.

Certain paullones analogs have been reported (Leost *et al.* 2000) to be GSK-3  
30      inhibitors. These compounds were proposed to be useful in the study and possible treatment of neurodegenerative and proliferative disorders.

3-Anilino-4-arylmaleimides have been reported to be potent and selective inhibitors of GSK-3 (Smith *et al.* 2001).

Hymenialdisine is an inhibitor of GSK-3. It was suggested to have potential in treating neurodegenerative disorders (Thunnissen *et al.* 2000).

5       The protein kinase C inhibitors GF1092 and Ro 31-8220 have been reported to be inhibitors of GSK-3 (Tavare *et al.* 1999).

Indirubines inhibit GSK-3 (Garnier *et al.* 2001). A potential application for the use of the indirubines as a treatment of neurodegenerative disorders was disclosed.

10       GSK-3 inhibitors SB-415286 and SB216763 protected both central and peripheral neurons grown in culture from death induced by reduced phosphatidyl inositol pathway activity (Cross *et al.* 2000).

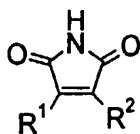
The use of these compounds to lowering and controlling normal or elevated intraocular pressure (IOP) and to treat glaucoma has not been disclosed.

15

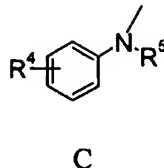
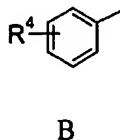
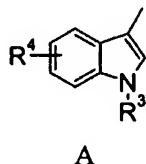
This invention is directed at the treatment of glaucoma by the inhibition of GSK-3. It is contemplated that any GSK-3 inhibiting compound will be useful in the methods of the present invention. The inventors contemplate that any of the compounds disclosed in WO 00/38675; WO 00/21927; Cogan *et al.* 2000; Leost *et al.* 2001; Smith *et al.* 2001; 20       Garnier *et al.* 2001; Cross *et al.* 2001; Thunnissen *et al.* 2000; Tavare *et al.* 1999 (as discussed above, all herein incorporated by reference) will be particularly useful.

In one preferred embodiment, the compound for use in the methods of the invention will be selected from compounds defined in WO 00/21927, EP 470490, WO 25       93/18766, WO 93/18765, EP 397060, WO 98/11103, WO 98/11102, WO 98/04552, WO 98/04551, DE 4243321, DE 4005970, DE 3914764, WO 96/04906, WO 95/07910, DE 4217964, US 5856517, US 5891901, WO 99/42100, EP 328026, EP 384349, EP 540956, DE 4005969, or EP 508792.

Preferred compounds include compounds of the formula:



wherein  $R^1$  and  $R^2$  independently =



5

$R^3$  = H,  $C_{1-6}$ alkyl, (un)substituted phenyl,  $C_{1-6}$ alkyl- $NR^6R^7$ ,  $C_{1-7}$ cycloalkyl,  $C_{1-6}$ alkyl- $OR^6$ ,  $C_{1-6}$ alkyl $C(O)_2R^5$ ,  $C_{1-6}$ alkyl $C(O)NR^6R^7$ ;

$R^4$  = H, or one or more substituents  $C_{1-6}$ alkyl, (un)substituted phenyl,  $-OR^6$ ,  $-SR^6$ ,  
 10 halogen, (un)substituted phenoxy,  $-CN$ ,  $-NO_2$ ,  $C_{1-6}$ alkyl- $NR^6R^7$ ,  $-NR^6R^7$ ,  $C_{1-7}$ cycloalkyl,  
 (un)substituted heterocyclyl,  $-C(O)_2R^5$ ,  $C_{1-6}$ alkyl $C(O)_2R^5$ ,  $C_{1-6}$ alkyl $C(O)NR^6R^7$ ; and

$R^5$ ,  $R^6$ ,  $R^7$  = H,  $C_{1-6}$ alkyl, (un)substituted phenyl.

15

Preferably,

$R^1$  = A, B;  $R^2$  = B, C;

$R^3$  = H,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl- $NR^6R^7$ ,  $C_{1-6}$ alkyl- $OR^6$ ,  $C_{1-6}$ alkyl $C(O)_2R^5$ ,  $C_{1-6}$ alkyl $C(O)NR^6R^7$ ;

$R^4$  = H, or one or more substituents  $C_{1-6}$ alkyl, (un)substituted phenyl,  $-OR^6$ , halogen,  
 (un)substituted phenoxy,  $-NO_2$ ,  $C_{1-6}$ alkyl- $NR^6R^7$ ,  $-NR^6R^7$ , (un)substituted heterocyclyl,  
 20  $-C(O)_2R^5$ ,  $C_{1-6}$ alkyl $C(O)_2R^5$ ,  $C_{1-6}$ alkyl $C(O)NR^6R^7$ ; and

$R^5$ ,  $R^6$ ,  $R^7$  = H,  $C_{1-3}$ alkyl.

The most preferred compounds for use in the methods of the invention include:

3-(1-[3-aminopropyl]-3-indoyl)-4-(2-chlorophenyl)pyrrole-2,5-dione and

25 3-(1-[3-hydroxypropyl]-3-indoyl)-4-(2-chlorophenyl)pyrrole-2,5-dione.

In other embodiments, compounds useful in the methods of the invention will be selected from the indirubine analogs defined in WO 01/37819. Generally preferred compounds include indirubine, 5-iodo-indirubine-3'-monoxime, 5-(hydroxyethylsulfonamide) indirubine, indirubine-3'-monoxime, 5-(methyl)sulfonamide indirubine, and 5-(dimethyl)sulfonamide indirubine.

Additional embodiments of the invention include the use of compounds selected from the 2,4-diaminothiazole analog defined in WO 01/37819. Preferred compounds include:

(4-amino-2-phenylaminothiazol-5-yl)cyclopropylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(4-fluorophenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)phenylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)pyridin-3-ylmethanone,  
1-(4-amino-2-phenylaminothiazol-5-yl)propan-1-one  
(4-amino-2-phenylaminothiazol-5-yl)-3,4-difluorophenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)-3-fluorophenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)naphthalen-2-ylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)biphenyl-4-ylmethanone,  
4-amino-2-phenylaminothiazol-5-yl)-(3-benzoyloxyphenyl)methanone,  
[4-amino-2-(4-bromophenylamino)thiazol-5-yl]cyclopropylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)-3,4-dichlorophenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)-3-methylbenzo[b]thiophen-2-yl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(2-methoxyphenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(3-methoxyphenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(4-methoxyphenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(4-chloro-3-methylphenyl)methanone,  
(4-amino-2-propylaminothiazol-5-yl)pyridin-3-yl-methanone,  
(4-amino-2-phenylaminothiazol-5-yl)pyridin-2-yl-methanone,  
(4-amino-2-phenylaminothiazol-5-yl)-pyridinyl-4-yl-methanone,  
(4-amino-2-phenylaminothiazol-5-yl)thiophen-2-yl-methanone,



(4-amino-2-phenylaminothiazol-5-yl)thiophen-3-ylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(2,6-difluorophenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(2,6-dichlorophenyl)methanone,  
1-(4-amino-2-phenylaminothiazol-5-yl)ethanone,  
5 [4-amino-2-(pyridin-3-ylamino)thiazol-5-yl]methanone,  
[4-amino-2-(pyridin-3-ylamino)thiazol-5-yl]phenylmethanone,  
[4-amino-2-(3-methoxypropylamino)thiazol-5-yl]pyridin-3-ylmethanone,  
3-[4-amino-5-(pyridine-3-carbonyl)thiazol-2-ylamino]butyric acid ethyl ester  
[4-amino-2-(3,4-dichlorophenylamino)thiazol-5-yl]-(3-benzyloxyphenyl)methanone,  
10 [4-amino-2-(4-chlorophenylamino)thiazol-5-yl]-(3-benzyloxyphenyl)methanone, and  
(4-amino-2-ethylaminothiazol-5-yl)phenylmethanone.

In still another embodiment, compounds selected from the 1,2,4-triazole-carboxylic acid derivative or analog defined in WO 01/09106 will be useful in the methods of the  
15 invention. Preferred 1,2,4-triazole-carboxylic acid derivatives include:

3-amino-5-anilino-2-benzoyl-1,2,4-triazole,  
3-amino-5-anilino-2-(3,4-methylenedioxybenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(3-*trans*-(2-furylacryloyl)-1,2,4-triazole,  
3-amino-5-anilino-1-(3-*trans*-(2-furylacryloyl)-1,2,4-triazole,  
20 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid phenylamide,  
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid cyclohexylamide,  
3-amino-5-anilino-1,2,4-triazole-1-carboxylic acid cyclohexylamide,  
3-amino-5-(5-chloro-2-methylanilino)-2-benzoyl-1,2,4-triazole,  
3-amino-5-anilino-2-(4-chlorobenzoyl)-1,2,4-triazole,  
25 3-amino-5-anilino-2-(2-naphthoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-phenylbenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-trifluoromethylbenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-((3-benzoyl)benzoyl)-1,2,4-triazole,  
30 3-amino-5-anilino-2-(4-biphenylacetyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(2-thienylacetyl)-1,2,4-triazole,

3-amino-5-(3-chloroanilino)-2-phenylthioacetyl-1,2,4-triazole,  
 3-amino-5-(3-chloroanilino)-2-(2-naphthylacetyl)-1,2,4-triazole,  
 3-amino-5-anilino-2-(phenoxybenzoyl)-1,2,4-triazole,  
 3-amino-5-(3-chloroanilino)-2-benzoyl-1,2,4-triazole,  
 5 3-amino-5-anilino-2-cyclohexylcarbonyl-1,2,4-triazole,  
 3-amino-5-anilino-2-phenylacetyl-1,2,4-triazole,  
 3-amino-5-anilino-2-(3-nicotinyl)-1,2,4-triazole,  
 3-amino-5-anilino-2-(3,5-dichlorobenzoyl)-1,2,4-triazole,  
 3-amino-5-anilino-2-(4-acetylbenzoyl)-1,2,4-triazole,  
 10 3-amino-5-anilino-2-(3-indolylacetyl)-1,2,4-triazole,  
 3-amino-5-anilino-2-(4-fluorophenylacetyl)-1,2,4-triazole,  
 3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole,  
 3-amino-5-(3-chloroanilino)-2-(3-benzoylpropanoyl)-1,2,4-triazole,  
 3-amino-5-anilino-2-(cyclopent-2-enyl)acetyl-1,2,4-triazole,  
 15 3-amino-5-(3-chloroanilino)-2-(3-benzoylbutyroyl)-1,2,4-triazole,  
 3-amino-5-(3-chloroanilino)-2-(3,3-diphenylpropanoyl)-1,2,4-triazole,  
 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid 4-biphenylamide,  
 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-phenoxyphenyl)amide,  
 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-bromo-2-methylphenyl)amide,  
 20 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (1-naphthyl)amide,  
 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-methoxyphenyl)amide,  
 3-amino-5-(4-methoxyanilino)-1,2,4-triazole-2-carboxylic acid (4-chlorophenyl)amide,  
 and  
 3,5-diamino-2-benzoyl-1,2,4-triazole.

25

Hymenialdisine or derivative or analog defined in WO 01/41768 may also be useful in certain embodiments of the invention. Preferred such compounds include:

Hymenialdisine (4-(2-amino-4-oxo-2-imidazolin-5-ylidene)-4,5,6,7-tetrahydropyrrolo(2,3-c)azepine-8-one),

30 4-(2-amino-4-oxo-2-imidazolin-5-ylidene)—2-bromo-4,5,6,7-tetrahydropyrrolo(2,3-c)azepine-8-one, and

(4-(2-amino-4-oxo-2-imidazolin-5-ylidene)—3-bromo-4,5,6,7-tetrahydropyrrolo(2,3-c)azepine-8-one.

Other embodiments of the invention include the use of paullone analogs, including  
5 9-nitropaullone, 9-bromopaullone, 9-chloropaullone, and 9-bromo-12-methoxycarbonylmethypaullone in the methods of the invention.

The Compounds of this invention, can be incorporated into various types of ophthalmic formulations for delivery to the eye (e.g., topically, intracamerally, or via an  
10 implant). The Compounds are preferably incorporated into topical ophthalmic formulations for delivery to the eye. The Compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving  
15 a Compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the Compound. Furthermore, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to  
20 improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the Compound in a  
25 hydrophilic base prepared from the combination of, for example, carbopol-974, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

The Compounds are preferably formulated as topical ophthalmic suspensions or  
30 solutions, with a pH of about 4 to 8. The establishment of a specific dosage regimen for each individual is left to the discretion of the clinicians. The Compounds will normally be

contained in these formulations in an amount 0.01% to 5% by weight, but preferably in an amount of 0.05% to 2% and most preferably in an amount 0.1 to 1.0% by weight. The dosage form may be a solution, suspension microemulsion. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the discretion of a skilled clinician.

The Compounds can also be used in combination with other agents for treating glaucoma, such as, but not limited to,  $\beta$ -blockers, prostaglandins, carbonic anhydrase inhibitors,  $\alpha_2$  agonists, miotics, and neuroprotectants.

The following examples are representative of the techniques employed by the inventors in carrying out aspects of the present invention. It should be appreciated that while these techniques are exemplary of preferred embodiments for the practice of the invention, those of skill in the art, in light of the present disclosure, will recognize that numerous modifications can be made without departing from the spirit and intended scope of the invention.

### Example 1

#### GSK-3 inhibition

Inhibition of GSK-3 can be assayed by the methods described in WO 00/38675. Compounds are evaluated for their ability to inhibit the phosphorylation of a biotinylated peptide derived from the peptide sequence for the phosphorylation site of glycogen synthase. Biot-KYRRAAVPPSPSLSRHSSPHQ(SP)EDEEE is used as the substrate peptide where (SP) is a prephosphorylated serine and S are the three consensus phosphorylation sites for GSK-3 specific phosphorylation. GSK-3 kinase (10nM final concentration) in a pH 7.0 MOPS buffer containing Tween-20 0.01%, glycerol 5%, 2-mercaptoethanol 7.5mM, magnesium acetate 10mM, substrate peptide 8  $\mu$ M, [ $\gamma$ -<sup>33</sup>P]-ATP 10  $\mu$ M and inhibitor are incubated at room temperature for 1 hour. The reaction is stopped by the addition of an aqueous mM EDTA solution containing Streptavidin coated SPA beads. Following centrifugation radioactivity is counted using a beta scintillation counter.

**Example 2****Inhibition of the FRP induced reduction in outflow rate and  $\beta$ -catenin levels in perfused anterior segments**

Human ocular anterior segments are perfused with Dulbecco's modified Eagle's medium (DMEM) at a constant pressure of 11 mm Hg. The outflow rate of each eye is measured by weighing its reservoir at specified periods. After a stabilization period, the eyes are perfused with either vehicle or FRP-1 (10  $\mu$ g/ml) and their outflow rates monitored for 2-5 days. The perfusion of FRP-1 caused a decrease in aqueous humor outflow. Inhibitor is added and the anterior segment is perfused for an additional 2-4 days. Outflow rate is measured by weighing its reservoir at specific periods.

**EXAMPLE 3**

<b>Ingredients</b>	<b>Amount (wt %)</b>
Compound of Example 1	0.01 – 2% **
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

15

**EXAMPLE 4**

<b>Ingredients</b>	<b>Amount (wt %)</b>
Compound of Example 1	0.01 – 2%
Methyl cellulose	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

5

**EXAMPLE 5**

<b>Ingredients</b>	<b>Amount (wt %)</b>
Compound of Example 1	0.01 – 2%
Guar gum	0.4- 6.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4
Purified water	q.s. to 100%

10

**EXAMPLE 6**

<b>Ingredients</b>	<b>Amount (wt %)</b>
Compound of Example 1	0.01 – 2%
White petrolatum and mineral oil and lanolin	Ointment consistency
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.3 – 7.4

5 All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both  
10 chemically and structurally related may be substituted for the agents described herein to achieve similar results. Such substitutions and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.  
15

**References**

The following references, to the extent that they provide exemplary procedural or  
5 other details supplementary to those set forth herein, are specifically incorporated herein  
by reference.

**Patents**

DE 3914764  
10 DE 4005969  
DE 4005970  
DE 4217964  
DE 4243321  
EP 328026  
15 EP 384349  
EP 397060  
EP 470490  
EP 508792  
EP 540956  
20 U.S. Patent No. 5,856,517  
U.S. Patent No. 5,891,901  
U.S. Patent No. 6,057,117  
WO 93/18765  
WO 93/18766  
25 WO 95/07910  
WO 96/04906  
WO 98/04551  
WO 98/04552  
WO 98/11102  
30 WO 98/11103  
WO 99/42100



WO 00/21927

WO 00/38675

WO 01/09106

WO 01/37819

5 WO 01/41768

WO 01/47533

WO 01/49709

WO 01/56567

10

### **Other References**

Bafico *et al.*, J. BIOL. CHEM., 274(23):16180-16187 (1999)

Leost *et al.*, EUR. J. BIOCHEM., 267:5983-5994 (2001)

Smith *et al.*, BIOORGANIC & MED. CHEM. LETTERS, 11:635-639 (2001)

Thunnissen *et al.*, CHEM. & BIO., 7:51-63 (2000)

15 Tavare *et al.*, FEBS LETTERS, 460:433-436 (1999)

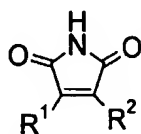
Cross *et al.*, J. NEUROCHEM., 77:94-102 (2001)

Coglan *et al.*, CHEM. & BIO., 7(10):793-803 (2000)

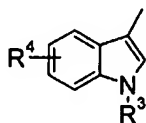
Garnier *et al.*, J. BIOL. CHEM., 276(1):251-260 (2001)

**We Claim:**

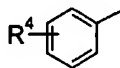
1. A method for treating glaucomatous optic neuropathy comprising administering to a patient in need thereof a therapeutically effective amount of a composition comprising at least one glycogen synthase kinase-3 (GSK-3) inhibitor in a pharmaceutically acceptable carrier.
2. The method of claim 1, wherein said GSK-3 inhibitor is a compound of the formula:



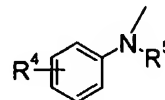
wherein  $R^1$  and  $R^2$  independently =



A



B



C

$R^3$  = H,  $C_{1-6}$ alkyl, (un)substituted phenyl,  $C_{1-6}$ alkyl- $NR^6R^7$ ,  $C_{1-7}$ cycloalkyl,  $C_{1-6}$ alkyl- $OR^6$ ,  $C_{1-6}$ alkyl $C(O)_2R^5$ ,  $C_{1-6}$ alkyl $C(O)NR^6R^7$ ;

$R^4$  = H, or one or more substituents  $C_{1-6}$ alkyl, (un)substituted phenyl,  $-OR^6$ ,  $-SR^6$ , halogen, (un)substituted phenoxy,  $-CN$ ,  $-NO_2$ ,  $C_{1-6}$ alkyl- $NR^6R^7$ ,  $-NR^6R^7$ ,  $C_{1-7}$ cycloalkyl, (un)substituted heterocyclyl,  $-C(O)_2R^5$ ,  $C_{1-6}$ alkyl $C(O)_2R^5$ ,  $C_{1-6}$ alkyl $C(O)NR^6R^7$ ; and

$R^5$ ,  $R^6$ ,  $R^7$  = H,  $C_{1-6}$ alkyl, (un)substituted phenyl.

3. The method of claim 2, wherein  
 $R^1 = A, B$ ;  $R^2 = B, C$ ;  
 $R^3 = H, C_{1-6}\text{alkyl}, C_{1-6}\text{alkyl}-NR^6R^7, C_{1-6}\text{alkyl}-OR^6, C_{1-6}\text{alkyl}C(O)_2R^5,$   
 $C_{1-6}\text{alkyl}C(O)NR^6R^7$ ;  
 $R^4 = H$ , or one or more substituents  $C_{1-6}\text{alkyl}$ , (un)substituted phenyl,  $-OR^6$ ,  
halogen, (un)substituted phenoxy,  $-NO_2$ ,  $C_{1-6}\text{alkyl}-NR^6R^7$ ,  $-NR^6R^7$ , (un)substituted  
heterocyclyl,  $-C(O)_2R^5$ ,  $C_{1-6}\text{alkyl}C(O)_2R^5$ ,  $C_{1-6}\text{alkyl}C(O)NR^6R^7$ ; and  
 $R^5, R^6, R^7 = H, C_{1-3}\text{alkyl}$ .
4. The method of claim 3, wherein said GSK-3 inhibitor is 3-(1-[3-aminopropyl]-3-indolyl)-4-(2-chlorophenyl)pyrrole-2,5-dione or 3-(1-[3-hydroxypropyl]-3-indolyl)-4-(2-chlorophenyl)pyrrole-2,5-dione.
5. The method of claim 1, wherein said GSK-3 inhibitor is a compound selected from the group consisting of indirubine analogs, 2,4-diaminothiazole analogs, 1,2,4-triazole-carboxylic acid derivatives or analogs, hymenialdesine or derivatives or analogs thereof, and paullone analogs.
6. The method of claim 5, wherein the GSK-3 inhibitor is an indirubine analog.
7. The method of claim 6, wherein the indirubine analog is selected from the group consisting of indirubine, 5-iodo-indirubine-3'-monoxime, 5-(hydroxyethylsulfonamide) indirubine, indirubine-3'-monoxime, 5-(methyl)sulfonamide indirubine, and 5-(dimethyl)sulfonamide indirubine.
8. The method of claim 5, wherein the GSK-3 inhibitor is a 2,4-diaminothiazole analog.
9. The method of claim 8, wherein the 2,4-diaminothiazole analog is selected from the group consisting of:  
(4-amino-2-phenylaminothiazol-5-yl)cyclopropylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(4-fluorophenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)phenylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)pyridin-3-ylmethanone,

1-(4-amino-2-phenylaminothiazol-5-yl)propan-1-one  
(4-amino-2-phenylaminothiazol-5-yl)-3,4-difluorophenylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)-3-fluorophenylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)naphthalen-2-ylmethanone,  
5 (4-amino-2-phenylaminothiazol-5-yl)biphenyl-4-ylmethanone,  
4-amino-2-phenylaminothiazol-5-yl-(3-benzyloxyphenyl)methanone,  
[4-amino-2-(4-bromophenylamino)thiazol-5-yl]cyclopropylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)-3,4-dichlorophenylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)-3-methylbenzo[b]thiophen-2-ylmethanone,  
10 (4-amino-2-phenylaminothiazol-5-yl)-(2-methoxyphenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(3-methoxyphenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(4-methoxyphenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(4-chloro-3-methylphenyl)methanone,  
(4-amino-2-propylaminothiazol-5-yl)pyridin-3-ylmethanone,  
15 (4-amino-2-phenylaminothiazol-5-yl)pyridin-2-ylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)-pyridinyl-4-ylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)thiophen-2-ylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)thiophen-3-ylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(2,6-difluorophenyl)methanone,  
20 (4-amino-2-phenylaminothiazol-5-yl)-(2,6-dichlorophenyl)methanone,  
1-(4-amino-2-phenylaminothiazol-5-yl)ethanone,  
[4-amino-2(pyridin-3-ylamino)thiazol-5-yl]methanone,  
[4-amino-2-(pyridin-3-ylamino)thiazol-5-yl]phenylmethanone,  
[4-amino-2-(3-methoxypropylamino)thiazol-5-yl]pyridin-3-ylmethanone,  
25 3-[4-amino-5(pyridine-3-carbonyl)thiazol-2-ylamino]butyric acid ethyl ester  
[4-amino-2-(3,4-dichlorophenylamino)thiazol-5-yl]-(3-benzyloxyphenyl)methanone,  
[4-amino-2-(4-chlorophenylamino)thiazol-5-yl]-(3-benzyloxyphenyl)methanone,  
and  
30 (4-amino-2-ethylaminothiazol-5-yl)phenylmethanone.

10. The method of claim 5, wherein the GSK-3 inhibitor is a 1,2,4-triazole-carboxylic acid derivative or analog.

11. The method of claim 10, wherein the 1,2,4-triazole-carboxylic acid derivative or analog is selected from the group consisting of:

- 5 3-amino-5-anilino-2-benzoyl-1,2,4-triazole,  
3-amino-5-anilino-2-(3,4-methylenedioxybenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(3-*trans*-(2-furylacryloyl)-1,2,4-triazole,  
3-amino-5-anilino-1-(3-*trans*-(2-furylacryloyl)-1,2,4-triazole,  
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid phenylamide,  
10 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid cyclohexylamide,  
3-amino-5-anilino-1,2,4-triazole-1-carboxylic acid cyclohexylamide,  
3-amino-5-(5-chloro-2-methylanilino)-2-benzoyl-1,2,4-triazole,  
3-amino-5-anilino-2-(4-chlorobenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(2-naphthoyl)-1,2,4-triazole,  
15 3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-phenylbenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-trifluoromethylbenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-((3-benzoyl)benzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-biphenylacetyl)-1,2,4-triazole,  
20 3-amino-5-anilino-2-(2-theinylacetyl)-1,2,4-triazole,  
3-amino-5-(3-chloroanilino)-2-phenylthioacetyl-1,2,4-triazole,  
3-amino-5-(3-chloroanilino)-2-(2-naphthylacetyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(phenoxybenzoyl)-1,2,4-triazole,  
3-amino-5-(3-chloroanilino)-2-benzoyl-1,2,4-triazole,  
25 3-amino-5-anilino-2-cyclohexylcarbonyl-1,2,4-triazole,  
3-amino-5-anilino-2-phenylacetyl-1,2,4-triazole,  
3-amino-5-anilino-2-(3-nicotinyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(3,5-dichlorobenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-acetylbenzoyl)-1,2,4-triazole,  
30 3-amino-5-anilino-2-(3-indolylacetyl)-1,2,4-triazole,

3-amino-5-anilino-2-(4-fluorophenylacetyl)-1,2,4-triazole,  
 3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole,  
 3-amino-5-(3-chloroanilino)-2-(3-benzoylpropanoyl)-1,2,4-triazole,  
 3-amino-5-anilino-2-(cyclopent-2-enyl)acetyl-1,2,4-triazole,  
 5 3-amino-5-(3-chloroanilino)-2-(3-benzoylbutyryl)-1,2,4-triazole,  
 3-amino-5-(3-chloroanilino)-2-(3,3-diphenylpropanoyl)-1,2,4-triazole,  
 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid 4-biphenylamide,  
 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-phenoxyphenyl)amide,  
 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-bromo-2-  
 10 methylphenyl)amide,  
 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (1-naphthyl)amide,  
 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-methoxyphenyl)amide,  
 3-amino-5-(4-methoxyanilino)-1,2,4-triazole-2-carboxylic acid (4-  
 chlorophenyl)amide, and  
 15 3,5-diamino-2-benzoyl-1,2,4-triazole.

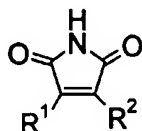
12. The method of claim 5, wherein the GSK-3 inhibitor is a hymenialdisine derivative or analog.

13. The method of claim 12, wherein the hymenialdesine derivative or analog is selected from the group consisting of:

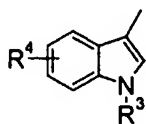
20 Hymenialdisine (4-(2-amino-4-oxo-2-imidazolin-5-ylidene)-4,5,6,7-  
 tetrahydropyrrolo(2,3-c)azepine-8-one),  
 4-(2-amino-4-oxo-2-imidazolin-5-ylidene)—2-bromo-4,5,6,7-  
 tetrahydropyrrolo(2,3-c)azepine-8-one, and  
 (4-(2-amino-4-oxo-2-imidazolin-5-ylidene)—3-bromo-4,5,6,7-  
 25 tetrahydropyrrolo(2,3-c)azepine-8-one.

14. The method of claim 5, wherein the GKS-3 inhibitor is a paullone analog.

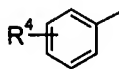
15. The method of claim 14, wherein the paullone analog is selected from the group consisting of 9-nitropaullone, 9-bromopaullone, 9-chloropaullone, and 9-bromo-12-methoxycarbonylmethypaullone in the methods of the invention.
16. The method of claim 1, wherein said administering is topical application, intracamerally or via an implant.
17. The method of claim 1, wherein the concentration of said GSK-3 inhibitor in said composition is from 0.01% to 2%.
18. A method for lowering intraocular pressure (IOP) in a patient in need thereof said method comprising administering to said patient a therapeutically effective amount of a composition comprising at least one glycogen synthase kinase-3 (GSK-3) inhibitor in a pharmaceutically acceptable vehicle.
19. The method of claim 18, wherein said GSK-3 inhibitor is a compound of the formula:



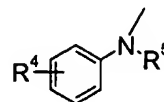
wherein R<sup>1</sup> and R<sup>2</sup> independently =



A



B



C

R<sup>3</sup> = H, C<sub>1-6</sub>alkyl, (un)substituted phenyl, C<sub>1-6</sub>alkyl-NR<sup>6</sup>R<sup>7</sup>, C<sub>1-7</sub>cycloalkyl, C<sub>1-6</sub>alkyl-OR<sup>6</sup>, C<sub>1-6</sub>alkylC(O)<sub>2</sub>R<sup>5</sup>, C<sub>1-6</sub>alkylC(O)NR<sup>6</sup>R<sup>7</sup>;

R<sup>4</sup> = H, or one or more substituents C<sub>1-6</sub>alkyl, (un)substituted phenyl, -OR<sup>6</sup>, -SR<sup>6</sup>, halogen, (un)substituted phenoxy, -CN, -NO<sub>2</sub>, C<sub>1-6</sub>alkyl-NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>R<sup>7</sup>, C<sub>1-</sub>

,cycloalkyl, (un)substituted heterocyclyl,  $-C(O)_2R^5$ ,  $C_{1-6}alkylC(O)_2R^5$ ,  $C_{1-6}alkylC(O)NR^6R^7$ ;

$R^5, R^6, R^7 = H, C_{1-6}alkyl, (un)substituted\ phenyl$ .

5

20. The method of claim 19, wherein

$R^1 = A, B; R^2 = B, C;$

$R^3 = H, C_{1-6}alkyl, C_{1-6}alkyl-NR^6R^7, C_{1-6}alkyl-OR^6, C_{1-6}alkylC(O)_2R^5, C_{1-6}alkylC(O)NR^6R^7;$

10

$R^4 = H, \text{ or one or more substituents } C_{1-6}alkyl, (un)substituted\ phenyl, -OR^6, \text{ halogen, (un)substituted phenoxy, } -NO_2, C_{1-6}alkyl-NR^6R^7, -NR^6R^7, (un)substituted\ heterocyclyl, -C(O)_2R^5, C_{1-6}alkylC(O)_2R^5, C_{1-6}alkylC(O)NR^6R^7; \text{ and } R^5, R^6, R^7 = H, C_{1-3}alkyl.$

15

21. The method of claim 20, wherein said GSK-3 inhibitor is 3-(1-[3-aminoprpyl]-3-indoyl)-4-(2-chlorophenyl) pyrrole-2,5-dione or 3-(1-[3-hydroxypropyl]-3-indoyl)-4-(2-chlorophenyl)pyrrole-2,5-dione.

20

22. The method of claim 18, wherein said GSK-3 inhibitor is a compound selected from the group consisting of indirubine analogs, 2,4-diaminothiazole analogs, 1,2,4-triazole-carboxylic acid derivatives or analogs, hymenialdesine or derivatives or analogs thereof, and paullone analogs.

23. The method of claim 22, wherein the GSK-3 inhibitor is an indirubine analog.

25

24. The method of claim 23, wherein the indirubine analog is selected from the group consisting of indirubine, 5-iodo-indirubine-3' monoxime, 5-(hydroxyethylsulfonamide) indirubine, indirubine-3'-monoxime, 5-(methyl)sulfonamide indirubine, and 5-(dimethyl)sulfonamide indirubine.

25. The method of claim 22, wherein the GSK-3 inhibitor is a 2,4-diaminothiazole analog.



26. The method of claim 25, wherein the 2,4-diaminothiazole analog is selected from the group consisting of:

(4-amino-2-phenylaminothiazol-5-yl)cyclopropylmethanone,

(4-amino-2-phenylaminothiazol-5-yl)-(4-fluorophenyl)methanone,

5 (4-amino-2-phenylaminothiazol-5-yl)phenylmethanone,

(4-amino-2-phenylaminothiazol-5-yl)pyridin-3-ylmethanone,

1-(4-amino-2-phenylaminothiazol-5-yl)propan-1-one

(4-amino-2-phenylaminothiazol-5-yl)-3,4-difluorophenyl)methanone,

(4-amino-2-phenylaminothiazol-5-yl)-3-fluorophenyl)methanone,

10 (4-amino-2-phenylaminothiazol-5-yl)naphthalen-2-ylmethanone,

(4-amino-2-phenylaminothiazol-5-yl)biphenyl-4-ylmethanone,

4-amino-2-phenylaminothiazol-5-yl)-(3-benzoyloxyphenyl)methanone,

[4-amino-2-(4-bromophenylamino)thiazol-5-yl]cyclopropylmethanone,

(4-amino-2-phenylaminothiazol-5-yl)-3,4-dichlorophenyl)methanone,

15 (4-amino-2-phenylaminothiazol-5-yl)-3-methylbenzo[b]thiophen-2-yl)methanone,

(4-amino-2-phenylaminothiazol-5-yl)-(2-methoxyphenyl)methanone,

(4-amino-2-phenylaminothiazol-5-yl)-(3-methoxyphenyl)methanone,

(4-amino-2-phenylaminothiazol-5-yl)-(4-methoxyphenyl)methanone,

(4-amino-2-phenylaminothiazol-5-yl)-(4-chloro-3-methylphenyl)methanone,

20 (4-amino-2-propylaminothiazol-5-yl)pyridin-3-yl-methanone,

(4-amino-2-phenylaminothiazol-5-yl)pyridin-2-yl-methanone,

(4-amino-2-phenylaminothiazol-5-yl)-pyridinyl-4-yl-methanone,

(4-amino-2-phenylaminothiazol-5-yl)thiophen-2-yl-methanone,

(4-amino-2-phenylaminothiazol-5-yl)thiophen-3-ylmethanone,

25 (4-amino-2-phenylaminothiazol-5-yl)-(2,6-difluorophenyl)methanone,

(4-amino-2-phenylaminothiazol-5-yl)-(2,6-dichlorophenyl)methanone,

1-(4-amino-2-phenylaminothiazol-5-yl)ethanone,

[4-amino-2(pyridin-3-ylamino)thiazol-5-yl]methanone,

[4-amino-2-(pyridin-3-ylamino)thiazol-5-yl]phenylmethanone,

30 [4-amino-2-(3-methoxypropylamino)thiazol-5-yl]pyridin-3-ylmethanone,

3-[4-amino-5(pyridine-3-carbonyl)thiazol-2-ylamino]butyric acid ethyl ester

[4-amino-2-(3,4-dichlorophenylamino)thiazol-5-yl]-(3-

benzyloxyphenyl)methanone,

[4-amino-2-(4-chlorophenylamino)thiazol-5-yl]-(3-benzyloxyphenyl)methanone,

and

(4-amino-2-ethylaminothiazol-5-yl)phenylmethanone.

27. The method of claim 22, wherein the GSK-3 inhibitor is a 1,2,4-triazole-carboxylic acid derivative or analog.

28. The method of claim 27, wherein the 1,2,4-triazole-carboxylic acid derivative or analog is selected from the group consisting of:

3-amino-5-anilino-2-benzoyl-1,2,4-triazole,

3-amino-5-anilino-2-(3,4-methylenedioxybenzoyl)-1,2,4-triazole,

3-amino-5-anilino-2-(3-*trans*-(2-furylacryloyl)-1,2,4-triazole,

3-amino-5-anilino-1-(3-*trans*-(2-furylacryloyl)-1,2,4-triazole,

3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid phenylamide,

3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid cyclohexylamide,

3-amino-5-anilino-1,2,4-triazole-1-carboxylic acid cyclohexylamide,

3-amino-5-(5-chloro-2-methylanilino)-2-benzoyl-1,2,4-triazole,

3-amino-5-anilino-2-(4-chlorobenzoyl)-1,2,4-triazole,

3-amino-5-anilino-2-(2-naphthoyl)-1,2,4-triazole,

3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole,

3-amino-5-anilino-2-(4-phenylbenzoyl)-1,2,4-triazole,

3-amino-5-anilino-2-(4-trifluoromethylbenzoyl)-1,2,4-triazole,

3-amino-5-anilino-2-((3-benzoyl)benzoyl)-1,2,4-triazole,

3-amino-5-anilino-2-(4-biphenylacetyl)-1,2,4-triazole,

3-amino-5-anilino-2-(2-theinylacetyl)-1,2,4-triazole,

3-amino-5-(3-chloroanilino)-2-phenylthioacetyl-1,2,4-triazole,

3-amino-5-(3-chloroanilino)-2-(2-naphthylacetyl)-1,2,4-triazole,

3-amino-5-anilino-2-(phenoxybenzoyl)-1,2,4-triazole,

3-amino-5-(3-chloroanilino)-2-benzoyl)-1,2,4-triazole,

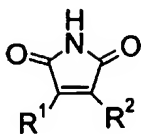
3-amino-5-anilino-2-cyclohexylcarbonyl-1,2,4-triazole,

3-amino-5-anilino-2-phenylacetyl-1,2,4-triazole,  
3-amino-5-anilino-2-(3-nicotinyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(3,5-dichlorobenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-acetylbenzoyl)-1,2,4-triazole,  
5 3-amino-5-anilino-2-(3-indolylacetyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-fluorophenylacetyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole,  
3-amino-5-(3-chloroanilino)-2-(3-benzoylpropanoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(cyclopent-2-enyl)acetyl-1,2,4-triazole,  
10 3-amino-5-(3-chloroanilino)-2-(3-benzoylbutyroyl)-1,2,4-triazole,  
3-amino-5-(3-chloroanilino)-2-(3,3-diphenylpropanoyl)-1,2,4-triazole,  
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid 4-biphenylamide,  
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-phenoxyphenyl)amide,  
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-bromo-2-  
15 methylphenyl)amide,  
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (1-naphthyl)amide,  
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-methoxyphenyl)amide,  
3-amino-5-(4-methoxyanilino)-1,2,4-triazole-2-carboxylic acid (4-  
chlorophenyl)amide, and  
20 3,5-diamino-2-benzoyl-1,2,4-triazole.

29. The method of claim 22, wherein the GSK-3 inhibitor is a hymenialdisine derivative or analog.

30. The method of claim 29, wherein the hymenialdesine derivative or analog is selected from the group consisting of:  
Hymenialdisine (4-(2-amino-4-oxo-2-imidazolin-5-ylidene)-4,5,6,7-tetrahydropyrrolo(2,3-c)azepine-8-one),  
5 4-(2-amino-4-oxo-2-imidazolin-5-ylidene)—2-bromo-4,5,6,7-tetrahydropyrrolo(2,3-c)azepine-8-one, and  
(4-(2-amino-4-oxo-2-imidazolin-5-ylidene)—3-bromo-4,5,6,7-tetrahydropyrrolo(2,3-c)azepine-8-one.
31. The method of claim 22, wherein the GKS-3 inhibitor is a paullone analog.
- 10 32. The method of claim 31, wherein the paullone analog is selected from the group consisting of 9-nitropaullone, 9-bromopaullone, 9-chloropaullone, and 9-bromo-12-methoxycarbonylmethypaullone in the methods of the invention.
33. The method of claim 18, wherein said administering is topical application, intracamerally or via an implant.
- 15 34. The method of claim 18, wherein the concentration of said GSK-3 inhibitor in said composition is from 0.01% to 2%.
35. The method of claim 18, wherein said patient suffers from glaucoma or ocular hypertension.
36. The method of claim 35, wherein said glaucoma is normal-tension glaucoma.
- 20 37. A method for preventing or inhibiting glaucomatous optic neuropathy and controlling IOP in a patient in need thereof, said method comprising at least one glycogen synthase kinase-3 (GSK-3) inhibitor in a pharmaceutically acceptable carrier.

38. The method of claim 37, wherein said GSK-3 inhibitor is a compound of the



formula:

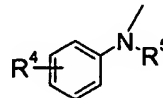
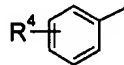
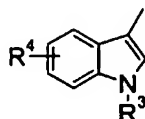
wherein R<sup>1</sup> and R<sup>2</sup> independently =

A

B

C

R<sup>3</sup> = H, C<sub>1-6</sub>alkyl, (un)substituted phenyl, C<sub>1-6</sub>alkyl-NR<sup>6</sup>R<sup>7</sup>, C<sub>1-7</sub>cycloalkyl,



C<sub>1-6</sub>alkyl-OR<sup>6</sup>, C<sub>1-6</sub>alkylC(O)<sub>2</sub>R<sup>5</sup>, C<sub>1-6</sub>alkylC(O)NR<sup>6</sup>R<sup>7</sup>;

R<sup>4</sup> = H, or one or more substituents C<sub>1-6</sub>alkyl, (un)substituted phenyl, -OR<sup>6</sup>,  
-SR<sup>6</sup>, halogen, (un)substituted phenoxy, -CN, -NO<sub>2</sub>, C<sub>1-6</sub>alkyl-NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>R<sup>7</sup>, C<sub>1-7</sub>cycloalkyl, (un)substituted heterocyclyl, -C(O)<sub>2</sub>R<sup>5</sup>, C<sub>1-6</sub>alkylC(O)<sub>2</sub>R<sup>5</sup>, C<sub>1-6</sub>alkylC(O)NR<sup>6</sup>R<sup>7</sup>; and

R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> = H, C<sub>1-6</sub>alkyl, (un)substituted phenyl.

39. The method of claim 38, wherein

R<sup>1</sup> = A, B; R<sup>2</sup> = B, C;

R<sup>3</sup> = H, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl-NR<sup>6</sup>R<sup>7</sup>, C<sub>1-6</sub>alkyl-OR<sup>6</sup>, C<sub>1-6</sub>alkylC(O)<sub>2</sub>R<sup>5</sup>, C<sub>1-6</sub>alkylC(O)NR<sup>6</sup>R<sup>7</sup>;

R<sup>4</sup> = H, or one or more substituents C<sub>1-6</sub>alkyl, (un)substituted phenyl, -OR<sup>6</sup>, halogen, (un)substituted phenoxy, -NO<sub>2</sub>, C<sub>1-6</sub>alkyl-NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>R<sup>7</sup>, (un)substituted heterocyclyl, -C(O)<sub>2</sub>R<sup>5</sup>, C<sub>1-6</sub>alkylC(O)<sub>2</sub>R<sup>5</sup>, C<sub>1-6</sub>alkylC(O)NR<sup>6</sup>R<sup>7</sup>; and

R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> = H, C<sub>1-3</sub>alkyl.

40. The method of claim 39, wherein said GSK-3 inhibitor is 3-(1-[3-aminoprpyl]-3-indoyl)-4-(2-chlorophenyl) pyrrole-2,5-dione or 3-(1-[3-hydroxypropyl]-3-indolyl)-4-(2-chlorophenyl)pyrrole-2,5-dione.
41. The method of claim 37, wherein said GSK-3 inhibitor is a compound selected  
5 from the group consisting of indirubine analogs, 2,4-diaminothiazole analogs, 1,2,4-triazole-carboxylic acid derivatives or analogs, hymenialdesine or derivatives or analogs thereof, and paullone analogs.
42. The method of claim 41, wherein the GSK-3 inhibitor is an indirubine analog.
43. The method of claim 42, wherein the indirubine analog is selected from the group  
10 consisting of indirubine, 5-iodo-indirubine-3'-monoxime, 5-(hydroxyethylsulfonamide) indirubine, indirubine-3'-monoxime, 5-(methyl)sulfonamide indirubine, and 5-(dimethyl)sulfonamide indirubine.
44. The method of claim 41, wherein the GSK-3 inhibitor is a 2,4-diaminothiazole analog.
45. The method of claim 44, wherein the 2,4-diaminothiazole analog is selected from  
15 the group consisting of:  
(4-amino-2-phenylaminothiazol-5-yl)cyclopropylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)-(4-fluorophenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)phenylmethanone,  
20 (4-amino-2-phenylaminothiazol-5-yl)pyridin-3-ylmethanone,  
1-(4-amino-2-phenylaminothiazol-5-yl)propan-1-one  
(4-amino-2-phenylaminothiazol-5-yl)-3,4-difluorophenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)-3-fluorophenyl)methanone,  
(4-amino-2-phenylaminothiazol-5-yl)naphthalen-2-ylmethanone,  
25 (4-amino-2-phenylaminothiazol-5-yl)biphenyl-4-ylmethanone,  
4-amino-2-phenylaminothiazol-5-yl)-(3-benzyloxyphenyl)methanone,  
[4-amino-2-(4-bromophenylamino)thiazol-5-yl]cyclopropylmethanone,  
(4-amino-2-phenylaminothiazol-5-yl)-3,4-dichlorophenyl)methanone,

(4-amino-2-phenylaminothiazol-5-yl)-3-methylbenzo[b]thiophen-2-yl)methanone,  
 (4-amino-2-phenylaminothiazol-5-yl)-(2-methoxyphenyl)methanone,  
 (4-amino-2-phenylaminothiazol-5-yl)-(3-methoxyphenyl)methanone,  
 (4-amino-2-phenylaminothiazol-5-yl)-(4-methoxyphenyl)methanone,  
 5 (4-amino-2-phenylaminothiazol-5-yl)-(4-chloro-3-methylphenyl)methanone,  
 (4-amino-2-propylaminothiazol-5-yl)pyridin-3-yl-methanone,  
 (4-amino-2-phenylaminothiazol-5-yl)pyridin-2-yl-methanone,  
 (4-amino-2-phenylaminothiazol-5-yl)-pyridinyl-4-yl-methanone,  
 (4-amino-2-phenylaminothiazol-5-yl)thiophen-2-yl-methanone,  
 10 (4-amino-2-phenylaminothiazol-5-yl)thiophen-3-ylmethanone,  
 (4-amino-2-phenylaminothiazol-5-yl)-(2,6-difluorophenyl)methanone,  
 (4-amino-2-phenylaminothiazol-5-yl)-(2,6-dichlorophenyl)methanone,  
 1-(4-amino-2-phenylaminothiazol-5-yl)ethanone,  
 [4-amino-2(pyridin-3-ylamino)thiazol-5-yl]methanone,  
 15 [4-amino-2-(pyridin-3-ylamino)thiazol-5-yl]phenylmethanone,  
 [4-amino-2-(3-methoxypropylamino)thiazol-5-yl]pyridin-3-ylmethanone,  
 3-[4-amino-5(pyridine-3-carbonyl)thiazol-2-ylamino]butyric acid ethyl ester  
 [4-amino-2-(3,4-dichlorophenylamino)thiazol-5-yl]-(3-benzyloxyphenyl)methanone,  
 20 [4-amino-2-(4-chlorophenylamino)thiazol-5-yl]-(3-benzyloxyphenyl)methanone,  
 and  
 (4-amino-2-ethylaminothiazol-5-yl)phenylmethanone.

46. The method of claim 41, wherein the GSK-3 inhibitor is a 1,2,4-triazole-carboxylic acid derivative or analog.
- 25 47. The method of claim 46, wherein the 1,2,4-triazole-carboxylic acid derivative or analog is selected from the group consisting of:
- 3-amino-5-anilino-2-benzoyl-1,2,4-triazole,  
 3-amino-5-anilino-2-(3,4-methylenedioxybenzoyl)-1,2,4-triazole,  
 3-amino-5-anilino-2-(3-*trans*-(2-furylacryloyl)-1,2,4-triazole,  
 30 3-amino-5-anilino-1-(3-*trans*-(2-furylacryloyl)-1,2,4-triazole,

3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid phenylamide,  
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid cyclohexylamide,  
3-amino-5-anilino-1,2,4-triazole-1-carboxylic acid cyclohexylamide,  
3-amino-5-(5-chloro-2-methylanilino)-2-benzoyl-1,2,4-triazole,  
5 3-amino-5-anilino-2-(4-chlorobenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(2-naphthoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-phenylbenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-trifluoromethylbenzoyl)-1,2,4-triazole,  
10 3-amino-5-anilino-2-((3-benzoyl)benzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-biphenylacetyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(2-theinylacetyl)-1,2,4-triazole,  
3-amino-5-(3-chloroanilino)-2-phenylthioacetyl-1,2,4-triazole,  
3-amino-5-(3-chloroanilino)-2-(2-naphthylacetyl)-1,2,4-triazole,  
15 3-amino-5-anilino-2-(phenoxybenzoyl)-1,2,4-triazole,  
3-amino-5-(3-chloroanilino)-2-benzoyl-1,2,4-triazole,  
3-amino-5-anilino-2-cyclohexylcarbonyl-1,2,4-triazole,  
3-amino-5-anilino-2-phenylacetyl-1,2,4-triazole,  
3-amino-5-anilino-2-(3-nicotinyl)-1,2,4-triazole,  
20 3-amino-5-anilino-2-(3,5-dichlorobenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-acetylbenzoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(3-indolylacetyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(4-fluorophenylacetyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(3-bromobenzoyl)-1,2,4-triazole,  
25 3-amino-5-(3-chloroanilino)-2-(3-benzoylpropanoyl)-1,2,4-triazole,  
3-amino-5-anilino-2-(cyclopent-2-enyl)acetyl-1,2,4-triazole,  
3-amino-5-(3-chloroanilino)-2-(3-benzoylbutyryl)-1,2,4-triazole,  
3-amino-5-(3-chloroanilino)-2-(3,3-diphenylpropanoyl)-1,2,4-triazole,  
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid 4-biphenylamide,  
30 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-phenoxyphenyl)amide,



- 3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (4-bromo-2-methylphenyl)amide,  
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (1-naphthyl)amide,  
3-amino-5-anilino-1,2,4-triazole-2-carboxylic acid (3-methoxyphenyl)amide,  
5 3-amino-5-(4-methoxyanilino)-1,2,4-triazole-2-carboxylic acid (4-chlorophenyl)amide, and  
3,5-diamino-2-benzoyl-1,2,4-triazole.
48. The method of claim 41, wherein the GSK-3 inhibitor is a hymenialdisine derivative or analog.
- 10 49. The method of claim 48, wherein the hymenialdesine derivative or analog is selected from the group consisting of:  
Hymenialdisine (4-(2-amino-4-oxo-2-imidazolin-5-ylidene)-4,5,6,7-tetrahydropyrrolo(2,3-c)azepine-8-one),  
4-(2-amino-4-oxo-2-imidazolin-5-ylidene)—2-bromo-4,5,6,7-tetrahydropyrrolo(2,3-c)azepine-8-one, and  
15 (4-(2-amino-4-oxo-2-imidazolin-5-ylidene)—3-bromo-4,5,6,7-tetrahydropyrrolo(2,3-c)azepine-8-one.
50. The method of claim 41, wherein the GKS-3 inhibitor is a paullone analog.
51. The method of claim 50, wherein the paullone analog is selected from the group  
20 consisting of 9-nitropaullone, 9-bromopaullone, 9-chloropaullone, and 9-bromo-12-methoxycarbonylmethypaullone in the methods of the invention.
52. The method of claim 37, wherein said administering is topical application, intracamerally or via an implant.
53. The method of claim 37, wherein the concentration of said GSK-3 inhibitor in said  
25 composition is from 0.01% to 2%.

54. The method of claim 37, wherein said patient suffers from glaucoma or ocular hypertension.
55. The method of claim 54, wherein said glaucoma is normal-tension glaucoma.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/30059

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C 12 N 9/99

US CL : 435/184

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**Minimum documentation searched (classification system followed by classification symbols)  
U.S. : 435/184

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
STN, WEST**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/62503 A2 (CENTRE NATIONAL DE RECHERCHE SCIENTIFIQUE) 09 December 1999 (09.12.99), abstract, page 9-10.	1-55
X	WO 01/37819 A2 (CENTRE NATIONAL DE RECHERCHE SCIENTIFIQUE) 31 May 2001 (31.05.01), abstract.	1-55



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

26 November 2002 (26.11.2002)

Date of mailing of the international search report

04 FEB 2003

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231  
Facsimile No. (703)305-3230

Authorized officer

Michael V. Meller

Telephone No. 703-268-0196